

## Value Changes in Bone Turnover Markers and Bone Mineral Density Using Ibandronate in Japanese Postmenopausal Osteoporotic Patients

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### Abstract

There have been no actual clinical reports on the changes in bone turnover markers and bone mineral density (BMD) during ibandronate (IBN) treatment with or without vitamin D in Japanese postmenopausal osteoporotic patients. In this study, 48 treatment-naïve primary osteoporotic patients were divided into the IBN group or IBN with alfacalcidol (ALF) group. Bone turnover markers, 1,25(OH)<sub>2</sub>D<sub>3</sub>, and whole parathyroid hormone (PTH) were examined just prior to treatment and at 1, 4, 8, 12, 16, and 20 weeks of therapy. BMD was measured at 0 and 16 weeks. Values of TRACP-5b were significantly and continuously lower than baseline after 1 week of treatment in both groups. TRACP-5b values were significantly lower in the IBN with ALF group than in the IBN alone group at 4 and 8 weeks of treatment. Values of BAP were comparable between the groups at all time points. Lumbar and hip BMD was slightly increased in both groups at 16 weeks of treatment, with no significant difference between both groups. We witnessed a significant reduction in bone markers in both treatment groups, as well as an increase in 1,25(OH)<sub>2</sub>D<sub>3</sub> and PTH in the IBN alone group.

**Keywords:** Bone mineral density; Bone turnover markers; Ibandronate; Osteoporosis

### Introduction

Osteoporosis is well known as a poly-factorial skeletal disorder characterized by low bone mineral density (BMD). Diminished BMD increases the risk of fracture to threaten both lifespan and quality of life. Thus, prevention of fracture is the primary therapeutic goal in osteoporosis [1].

Osteoporosis therapy is selected based on considerations of efficacy, safety, cost, and convenience. Bisphosphonates (BPs) are commonly prescribed to prevent and manage osteoporosis as a first-line treatment [2]. However, Rakel et al. have reported that patients should not lie down for 60 min before the first food or drink which could reduced patient compliance [3]. Alternatively, ibandronate (IBN) can be infused intravenously to enhance its bioavailability to as high as 100% [4].

The efficacy of IBN on vertebral fracture prevention has been demonstrated in postmenopausal osteoporosis [5,6]. Paggiosi et al. reported that IBN or alendronate (ALN) increased lumbar as well as total body BMD to a greater extent than did risedronate (RIS), while peripheral BMD did not differ among the BPs [7]. Since the effectiveness of ALN in the increase of BMD and fracture prevention is well defined [8], IBN may also represent a good choice for osteoporotic patients who are candidates for ALN.

According to the Phase III BONE study, 2.5 mg daily oral IBN provided a 49% risk reduction of vertebral fracture after 3 years of treatment [9]. In addition, no atypical fracture or osteonecrosis of the jaw was detected in this clinical trial. IBN has a lower affinity for

hydroxyapatite than other BPs apart from RIS [4]. Therefore, it might be a better option for osteoporotic treatment from the viewpoint of fewer adverse effects.

Since there are no clinical reports on the changes in bone turnover markers on BMD during IBN treatment with or without vitamin D in Japanese postmenopausal osteoporotic patients, we performed the following study. This investigation established and compared 2 test groups, the IBN alone group and the IBN plus alfacalcidol (ALF) group, as there is little information on the significance of active vitamin D addition to IBN in the treatment of post-menopausal osteoporotic patients, although: 1) in most osteoporosis studies, vitamin D and calcium (Ca) have been prescribed together [10], 2) elderly Japanese women typically have insufficient serum 25(OH)D [11], and 3) active vitamin D is more widely used in Japan than abroad [12]. We examined the laboratory results of 4 months of IBN treatment either alone or with ALF supplementation on lumbar and the average of bilateral hip BMDs (L-BMD and H-BMD, respectively), bone turnover markers, 1,25(OH)<sub>2</sub>D<sub>3</sub>, and whole parathyroid hormone (PTH) in Japanese osteoporotic patients.

### Subjects and Methods

Forty-eight treatment-naïve postmenopausal osteoporotic patients were prospectively recruited from our institutions between April 2014 and January 2015. The subjects were randomly divided into the IBN group (26 women, mean ± SD age: 76.6 ± 4.7 years) or the IBN with ALF group (22 women, mean ± SD age: 74.0 ± 9.0 years) using an enveloped method. Patient characteristics prior to IBN treatment are summarized in Table 1. No significant differences were found between the groups regarding to age or BMD. Furthermore, no patient had a history of medication that may have affected bone or calcium

metabolism, although 10 cases in the IBN group and 15 cases in the IBN with ALF group had hypertension and/or hyperlipidemia. Patients who had experienced a bone fracture less than 1 year prior to this study were excluded. The diagnosis of primary osteoporosis was made in accordance with the revised criteria established by the Japanese Society of Bone and Mineral Research [13]. All subjects received 1.0 mg IBN by intravenous (IV) injection every month. In the IBN with ALF group, daily 0.5 µg ALF was prescribed after every morning meal.

Variable (unit)	IBN Group	Variable (unit)	IBN with ALF Group
Cases	26 (All female )	Cases	22 (All female)
Age	76.6 ± 4.7	Age	74.0 ±
L-BMD (g/cm <sup>2</sup> )	0.70 ± 0.12	L-BMD (g/cm <sup>2</sup> )	0.69 ± 0.08
H-BMD (g/cm <sup>2</sup> )	0.70 ± 0.13	H-BMD (g/cm <sup>2</sup> )	0.66 ± 0.07
Past fractures	1 case: Ankle fracture	Past fractures	2 cases: Distal radial fracture
	5 cases: Vertebral fracture		1 case: Knee fracture
	1 case: Distal radial fracture		3 cases: Proximal femoral fracture
Pre-treatment	None	Pre-treatment	None
Complication with hypertension and/or hyperlipidemia	10 cases	Complication with hypertension and/or hyperlipidemia	15 cases

**Table 1:** Baseline patient characteristics in the IBN group and IBN with ALF group prior to treatment.

Serum bone alkaline phosphatase (BAP) and N-terminal propeptide of type 1 procollagen (P1NP) were measured as bone formation markers using a chemiluminescent enzyme immunoassay and antibody radioimmunoassay, respectively. Serum tartrate-resistant acid phosphatase (TRACP)-5b was determined as a marker of bone resorption using the enzyme-linked immunosorbent assay (ELISA). Serum whole PTH and 1,25(OH)<sub>2</sub>D<sub>3</sub> were assessed as bone turnover markers by immunoradiometric assays. Each marker was measured just prior to IBN administration and at 1, 4, 8, 12, 16, and 20 weeks of IBN treatment. After overnight fasting, serum and first void urine samples were collected between 8:30 a.m. and 10:00 a.m. Immunoassays were performed by SRL, Inc. (Tokyo, Japan). The scores of the bone turnover markers were presented on a logarithmic scale since they were not normally distributed, while values for whole PTH and 1,25(OH)<sub>2</sub>D<sub>3</sub> were shown as measured values.

BMD was measured using a Dual-energy X-ray Absorption (DXA) fan-beam bone densitometer (Lunar Prodigy; GE Healthcare, Waukesha, WI, USA) at the L1-4 levels of the spine and as the average of both hips.

For both groups, we compared the changes in each marker at each time point using linear mixed models. Each marker value and corresponding increase ratios (IRs) were individually adopted as a response variable: the use of ALF, the timing of the measurement, and those interactions were used as fixed effects, while the individuality of the measurement was adopted as a random effect. Of the 48 patients, L-BMD was measured in 28 patients before and 24 patients at 16 weeks

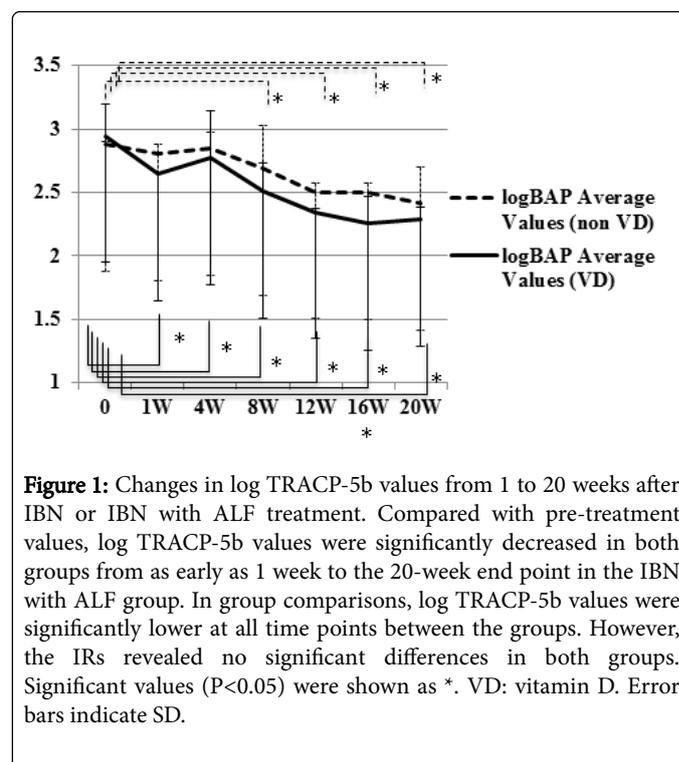
of treatment, and H-BMD was determined in 30 patients before and 28 patients at 16 weeks of treatment. The BMD values were evaluated as described above. Note that a simple linear model was used since the IRs were measured only at 16 weeks. P<0.05 was considered as significant.

This study was approved by the institutional ethical review board prior to its start and written informed consent was obtained from all subjects at Showa-Inan General Hospital. This study was carried out in accordance with the approved guidelines, and has also been approved by ClinicalTrials.gov (#IB2014). The date of registration was June 1, 2014.

## Results

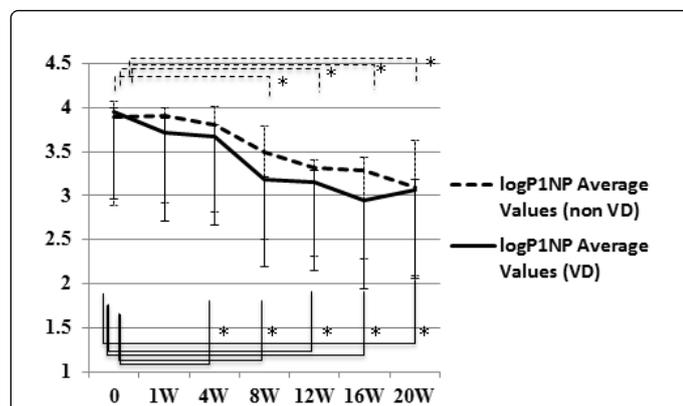
### Bone turnover markers

**Bone formation markers:** In time point comparisons, both log BAP and log P1NP values decreased gradually during treatment in the IBN group, with significant reductions recorded from 8 to 20 weeks (Figures 1 and 2). In the IBN with ALF group, log BAP values were decreased to a significant degree from 4 to 20 weeks (Figure 1) and log P1NP values became significantly reduced from 8 to 20 weeks (Figure 2). The IR of log BAP values was significantly decreased at 16 weeks of treatment in the IBN with ALF group, while no significant differences were found for the IR of P1NP in either group (data not shown).

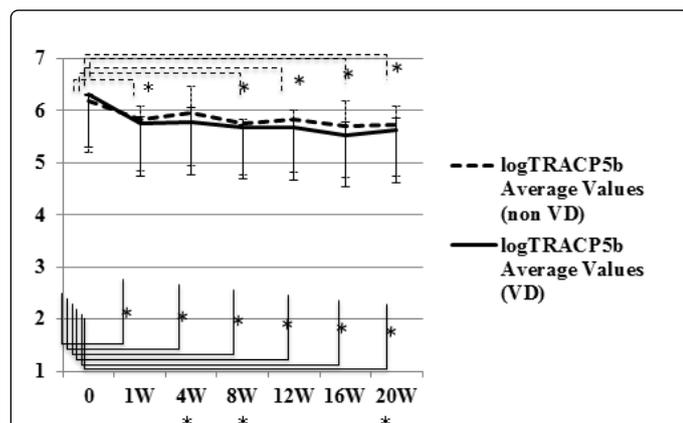


**Figure 1:** Changes in log TRACP-5b values from 1 to 20 weeks after IBN or IBN with ALF treatment. Compared with pre-treatment values, log TRACP-5b values were significantly decreased in both groups from as early as 1 week to the 20-week end point in the IBN with ALF group. In group comparisons, log TRACP-5b values were significantly lower at all time points between the groups. However, the IRs revealed no significant differences in both groups. Significant values (P<0.05) were shown as \*. VD: vitamin D. Error bars indicate SD.

With respect to data comparisons data between the groups, log BAP values were significantly lower from 8 to 20 weeks in the IBN group and from 4 to 20 weeks in the IBN with ALF group (Figure 1). Log P1NP values were significantly lower from 8 to 20 weeks in the IBN group and from 4 to 20 weeks in the IBN with ALF group (Figure 2). Comparisons of IRs showed no significant differences in log BAP or P1NP values in either group (data not shown).



**Figure 2:** Changes in log BAP values from 1 to 20 weeks after IBN or IBN with ALF treatment. Compared with pre-treatment values, log BAP values decreased gradually during treatment in the IBN group, with significant reductions recorded from 8 to 20 weeks. In the IBN with ALF group, log BAP values were decreased to a significant degree from 4 to 20 weeks. In group comparisons, log BAP values were significantly lower from 8 to 20 weeks in the IBN group and from 4 to 20 weeks in the IBN with ALF group. Significant values ( $P < 0.05$ ) are shown as \*. VD: vitamin D. Error bars indicate SD.



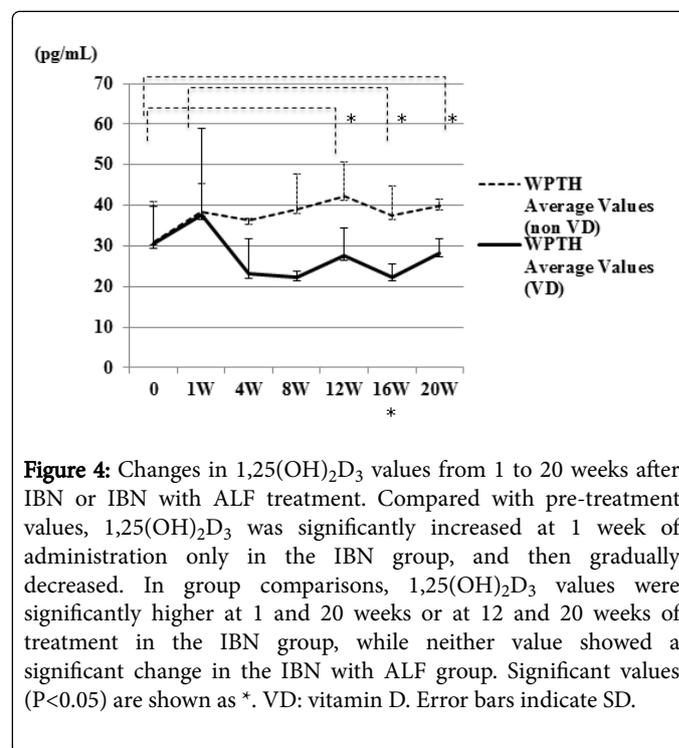
**Figure 3:** Changes in log PINP values from 1 to 20 weeks after IBN or IBN with ALF treatment. Compared with pre-treatment values, log PINP values decreased gradually during treatment in the IBN group, with significant reductions recorded from 8 to 20 weeks. In the IBN with ALF group, log PINP values became significantly reduced from 8 to 20 weeks. In group comparisons, log PINP values were significantly lower from 8 to 20 weeks in the IBN group and from 4 to 20 weeks in the IBN with ALF group. Significant values ( $P < 0.05$ ) are shown as \*. VD: vitamin D. Error bars indicate SD.

**Bone resorption markers:** In time point comparisons, log TRACP-5b values were significantly decreased in both groups from as early as 1 week to the 20-week end point in the IBN with ALF group (Figure 3). With respect to data comparisons between the groups, the IRs of log TRACP-5b values were significantly decreased at 4 and 8 weeks of treatment in the IBN with ALF group over the IBN group (data not shown). These results indicated an immediate and strong anti-resorptive effect of IBN as well as of IBN plus ALF.

With respect to data comparisons between the groups, log TRACP-5b values were significantly lower at all time points in both groups (Figure 3). However, IRs revealed no significant differences (Figure 3).

### Serum whole PTH and $1,25(\text{OH})_2\text{D}_3$

Whole PTH was significantly increased at 1 week and later at 12, 16, and 20 weeks of treatment in the IBN group, while there was no significant difference in the IBN plus ALF group (Figure 4). In time point comparisons,  $1,25(\text{OH})_2\text{D}_3$  was significantly increased at 1 week of administration only in the IBN group, and then gradually decreased (Figure 5). The IR of  $1,25(\text{OH})_2\text{D}_3$  values was significantly decreased at 1 week of therapy in the IBN with ALF group and that of whole PTH was not significantly changed (data not shown).

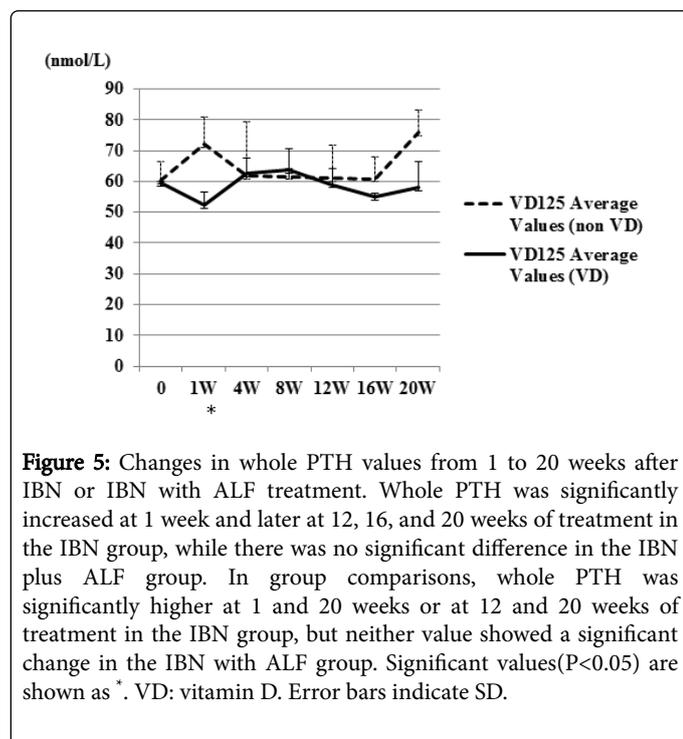


**Figure 4:** Changes in  $1,25(\text{OH})_2\text{D}_3$  values from 1 to 20 weeks after IBN or IBN with ALF treatment. Compared with pre-treatment values,  $1,25(\text{OH})_2\text{D}_3$  was significantly increased at 1 week of administration only in the IBN group, and then gradually decreased. In group comparisons,  $1,25(\text{OH})_2\text{D}_3$  values were significantly higher at 1 and 20 weeks or at 12 and 20 weeks of treatment in the IBN group, while neither value showed a significant change in the IBN with ALF group. Significant values ( $P < 0.05$ ) are shown as \*. VD: vitamin D. Error bars indicate SD.

With respect to data comparisons between the groups, the  $1,25(\text{OH})_2\text{D}_3$  and whole PTH values were significantly higher at 1 and 20 weeks or at 12 and 20 weeks of treatment in the IBN group, respectively, but neither value showed a significant change in the IBN with ALF group (Figure 4 and 5). Comparisons of IRs revealed no significant differences in  $1,25(\text{OH})_2\text{D}_3$  at any time point in either group, while whole PTH was significantly higher at 1 and 16 weeks of treatment (data not shown).

The mean  $\pm$  SD values of H-BMD in the IBN group just prior and at 16 weeks of treatment were  $0.70 \pm 0.13 \text{ g/cm}^2$  and  $0.70 \pm 0.12 \text{ g/cm}^2$ , respectively. The mean  $\pm$  SD values of L-BMD in the IBN group just prior and at 16 weeks of treatment were  $0.83 \pm 0.03 \text{ (g/cm}^2\text{)}$  and  $0.82 \pm 0.03 \text{ (g/cm}^2\text{)}$ , respectively. These values in the IBN with ALF group were  $0.66 \pm 0.07 \text{ g/cm}^2$  and  $0.69 \pm 0.08 \text{ g/cm}^2$  and  $0.82 \pm 0.13 \text{ g/cm}^2$  and  $0.85 \pm 0.12 \text{ g/cm}^2$ , respectively. Although the IRs of IBN patients showed changes of -1.30% for L-BMD and 0.56% for H-BMD and those of combined therapy were 3.81% for L-BMD and 5.14% for H-

BMD, there were no statistical differences among values or IRs at any time point in either group.



**Figure 5:** Changes in whole PTH values from 1 to 20 weeks after IBN or IBN with ALF treatment. Whole PTH was significantly increased at 1 week and later at 12, 16, and 20 weeks of treatment in the IBN group, while there was no significant difference in the IBN plus ALF group. In group comparisons, whole PTH was significantly higher at 1 and 20 weeks or at 12 and 20 weeks of treatment in the IBN group, but neither value showed a significant change in the IBN with ALF group. Significant values ( $P < 0.05$ ) are shown as \*. VD: vitamin D. Error bars indicate SD.

## Discussion

This study described the short-term results of IBN alone or IBN with ALF treatment in Japanese osteoporotic patients. We observed that IBN plus ALF improved bone turnover markers more significantly than IBN alone, although there were no significant changes in BMD values in either group at the study end point. Thus, IBN may represent a good first-line osteoporotic drug, preferably with vitamin D supplementation.

In a randomized, double-blinded study of Japanese osteoporotic patients (the MOVER study), monthly IV IBN was comparable to daily oral RIS in reducing the incidence of vertebral fracture [14]. Here, no patient experienced a fracture during our investigation, although the observational period of 4 months was too short to reach any definite conclusions.

Shiraki et al. reported that serum  $1,25(\text{OH})_2\text{D}_3$  and PTH levels peaked at 4 weeks of ALN treatment and then gradually decreased [8]. The reasons for these changes were speculated as diminished Ca and increased active vitamin D caused: 1) an increase in PTH receptors [15], 2) accelerated PTH action, 3) an increase in Ca, and 4) subsequent decreased PTH and  $1,25(\text{OH})_2\text{D}_3$  levels. Our study showed that IBN decreased Ca, which increased whole PTH in both groups because of negative feedback. Thereafter, however whole PTH gradually increased in the IBN group while it gradually decreased in the IBN with ALF group (Figure 5) due to ALF's effects on Ca metabolism. Since PTH stimulates  $1,25(\text{OH})_2\text{D}_3$  levels,  $1,25(\text{OH})_2\text{D}_3$  increased transiently at 1 week in the IBN group (data not shown), and then returned to baseline levels (Figure 5). On the contrary,  $1,25(\text{OH})_2\text{D}_3$  decreased transiently at 1 week in the IBN with ALF group since ALF is an active vitamin D, which potentially increased serum Ca levels (data not shown).

Another double-blinded clinical trial in Japan revealed increases in L-BMD and H-BMD of 5.1% and 1.7%, respectively, at 6 months of combined therapy with IV IBN and eldcalcitol [16]. Our study showed that the IR of IBN alone was -1.30% for L-BMD and 0.56% for H-BMD, while that of IBN with ALF was 3.81% for L-BMD and 5.14% for H-BMD, although there were no statistical differences among values or IRs at any time point in either group. Combined therapy with IV IBN and ALF might therefore be effective with respect to improving BMD. However, longer use of IBN for more than 6 months may be necessary to significantly improve BMD. Orimo et al. examined the efficacy and safety of ALN plus ALF versus ALN alone in a randomized controlled trial. Although they found no advantage for combined therapy for overall vertebral fracture prevention, ALN plus ALF was more effective for fracture prevention in patients with severe vertebral deformity or multiple prevalent vertebral fractures as well as for non-vertebral weight-bearing bone fracture prevention [17].

Senn et al. described that in postmenopausal women with osteoporosis, 2-year treatment with teriparatide (TPTD) led to a significantly larger increase in spine BMD than did IBN, suggesting that TPTD had more pronounced effects on bone microarchitecture [18]. Marcus et al. reported that daily TPTD increased spine BMD by approximately 4% over a median of 19 months [19]. Although TPTD apparently raises BMD more effectively than does IBN, these data were from American osteoporotic patients. The present study showed that IBN plus ALF increased L-BMD by 3.81% in Japanese osteoporotic patients at 4 months of treatment. Since this gain was not significant, more than 4 months of therapy may be required to improve BMD.

Very recently, Nakamura et al. released the "MOVEST study" in Japan and reported no significant differences between oral IBN of 100 mg/month and IV IBN of 1 mg/month with respect to increasing L-BMD in Japanese patients with primary osteoporosis [20]. Thus, oral IBN dosage may become more predominant in the future.

The limitations of this study are a relatively small cohort size and a short-term observational period. Further trials are needed to validate our results, especially with respect to increasing BMD values with IBN with or without ALF.

In conclusion, this investigation elucidated the changes in vitamin D<sub>3</sub>, PTH, and other bone markers by IBN with or without active vitamin D. We witnessed a significant reduction in bone markers in both treatment groups, as well as an increase in vitamin D<sub>3</sub> and PTH in the IBN alone group.

## Authors' Contributions

YN directed this study. SI, YT, MK, US, and HK conceived the study, and participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

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